EXHIBIT F

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United States District Court,
D. Delaware.
BIO-TECHNOLOGY GENERAL CORP., Plaintiff,
v.
Novo Nordisk A/S and NOVO NORDISK PHARMACEUTICALS, INC., Defendants.
No. Civ.02-235-SLR.

Aug. 3, 2004.

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Frederick L. Cottrell, III, and Jeffrey L. Moyer, of Richards, Layton & Finger, Wilmington, Delaware, for Defendants, Albert L. Jacobs, Jr., Daniel A. Ladow, Eugene C. Rzucidlo, and Joseph M. Manak, Elizabeth S. Lapadula, Beverly Lubit, Magnus Essunger, Jenifer Shahan, of Greenberg Traurig, LLP, New York, New York, of counsel.

OPINION

ROBINSON, Chief J.

I. INTRODUCTION

*1 Plaintiff Bio-Technology General Corp. ("BTG") appeals the decision of the Board of Patent Appeals and Interferences (the "Board") of the United States Patent and Trademark Office ("PTO") in *Blumberg v. Dalboge,* Interference No. 104,422, pursuant to 35 U.S.C. § 146. The Board granted the benefit of priority of invention for the subject matter of the interference count generally directed to ripe human growth hormone ("ripe hGH") to defendants Novo Nordisk A/S and Novo Nordisk Pharmaceuticals, Inc. (collectively, "Novo"). As a result of this priority award, Novo maintained its United States Patent No. 5,633,352 (the " '352 patent") and BTG was denied entitlement to a patent based upon its United States Application No. 09/023,248 (the " '248 application"). The court has jurisdiction over this suit pursuant to 28 U.S.C. § § 1331, 1338. The following are the court's findings of fact and conclusions of law pursuant to Fed.R.Civ.P. 52(a).

II. FINDINGS OF FACT

A. The Parties

1. BTG is a corporation organized under the laws of the State of Delaware with its principal place of business in Iselin, New Jersey. (D.I. 1 at ¶ 3)

2. Novo Nordisk A/S is a corporation organized under the laws of the Kingdom of Denmark with its principal place of business in Bagsvaerd, Denmark. (D.I. 1 at ¶ 4; D.I. 7 at ¶ 4)

3. Novo Nordisk Pharmaceuticals, Inc. is a corporation organized under the laws of the State of Delaware with its principal place of business in Princeton, New Jersey. (D.I. 1 at ¶ 5; D.I. 7 at ¶ 5)

B. The Technology in General

4. Proteins and peptides consist of chains of amino acids. (BTX 3 at 4) The amino acids are selected from the group of about twenty naturally occurring cellular amino acids. (*Id.*) The left-hand end of the amino acid chain is referred to as the N-terminus, and the right-hand end of the chain is referred to as the C-terminus.

5. Genes are comprised of long chains of DNA, which consist of nucleotide triplets. (*Id.*) These nucleotide triplets are referred to as codons. (*Id.*) When a particular protein is to be synthesized, messenger RNA ("mRNA") copy the region of the DNA that codes for the protein (i.e., the codons specific to the protein). (*Id.*) The mRNA are then used by the cell as a pattern to produce the protein. (*Id.*)

6. A cell seldomly synthesizes a desired protein directly. (*Id.* at 5) Rather, the first product, commonly referred to as a "fusion protein," typically consists of the final protein plus a pro-sequence. (*Id.*) The pro-sequence consists of additional amino acids attached to the N-terminus of the final desired protein. (*Id.*) To obtain the final desired protein, proteolytic enzymes cleave the peptide bonds

between the pro-sequence and the final desired protein. (*Id.* at 7)

7. Two types of proteolytic enzymes may be employed in protein synthesis: (1) exoproteases; and (2) endoproteases. Exoproteases cleave amino acids from the end of a protein chain at either the N-terminus or the C-terminus. Endoproteases, in contrast, cleave amino acids in the interior of a protein chain.

***2** 8. Aminopeptidases are exoproteases and cleave amino acids from the N-terminus of a protein chain. *Aeromonas,* Aminopeptidase I ("AP I"), leucine aminopeptidase ("LAP"), and dipeptidyl aminopeptidase I ("DAP I") are four distinct aminopeptidases.

9. LAP has the enzyme classification number E.C. 3.4.11.1. It releases amino acids sequentially one-by-one from the N-terminus of a peptide by hydrolizing the amide bonds found in the peptide. (BTX 319) LAP is known to have an optimal pH in the range of 7.5-9.0 and is unstable in the region of 4 to 5. (BTX 23; BTX 318) If the peptide to be cleaved by LAP contains a proline residue, LAP will not cleave the amino acid that precedes the proline residue because LAP is unable to hydrolize the bond that exists between the proline residue and the preceding amino acid. (DTX 319 at 433)

10. DAP I has the enzyme classification number E.C. 3.4.14.1 and is also referred to as cathepsin C. It releases amino acids sequentially in dipeptidyl units from the N-terminus of a peptide. It is known to have an optimum pH in the range of 4 to 6. (BTX 23)

C. Human Growth Hormone

11. Human growth hormone ("hGH") is a specific protein consisting of 191 amino acids. It is naturally secreted by the pituitary gland. (Paper 124 at 2) Proline is the second to last amino acid located at the N-terminus. The amino acid sequence for hGH is shown in the figure below.

TABULAR OR GRAPHIC MATERIAL SET AT THIS POINT IS NOT DISPLAYABLE

12. Human growth hormone is administered to treat conditions such as dwarfism, infertility, wound care, and intoxication. (BTX 36 at NNG0025821)

13. Pituitary-derived hGH may contain contaminants that cause a variety of diseases such as Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, and Kuru. ('352 patent, col. 3 at ll. 42-46) The risk of these diseases has lead some countries to ban the use of pituitary-derived hGH (BTX 36 at NNG0025821) For this reason, the need arose to produce hGH synthetically using recombinant DNA technology.

14. There are two basic approaches to make hGH using recombinant DNA technology: (1) an enzymatic cleavage system; and (2) a secretion system.

a. Enzymatic Cleavage System

15. In this approach, the gene for hGH is transferred to a host organism, such as the *E. coli* bacteria. The *E. coli* bacteria are transformed to express the fusion protein consisting of hGH with pro-sequence attached to the N-terminus. ('352 patent, col. 3 at ll. 26-29) The pro-sequence is cleaved from the fusion protein using an exopeptidase to form biosynthetic --> hGH. The following scheme shows this enzymatic cleavage system:

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          enzyme
A--hGH              hGH
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where A is a pro-sequence. (BTX 23)

16. If LAP is selected as the cleavage enzyme, cleavage terminates at the amino acid preceding proline, as noted above, leaving hGH as the final product. (*Id.*) The concept of using proline in conjunction with LAP to control the recombinant DNA synthesis of hGH is referred to as the "Y-pro stop signal strategy."

b. Secretion System

***3** 17. In this approach, host organisms such as yeast are transformed so that they express a pre-protein consisting of the desired protein with a leader or signal sequence attached to the N-terminus. The pre-protein is transported through the cell membrane. During transport, an endopeptidase, referred to as a "signal peptidase," clips off the leader sequence. The desired protein then is

secreted outside the cell.

18. Human growth hormone is expressed in the human pituitary gland as a pre-protein having a 26-amino acid leader sequence. The pre-hGH is transported through the cell membrane where the 26-amino acid leader sequence is clipped off. The desired 191-amino acid hGH then is secreted outside the human pituitary gland.

D. Novo's '352 Patent

19. The '352 patent, entitled "Biosynthetic Human Growth Hormone," was filed on March 10, 1995.

20. The '352 patent was granted on May 27, 1997.

21. The named inventors include Henrik Dalboge, John Pedersen, Thorkild Christensen, Jorli W. Ringsted, and Torben E. Jessen.

22. The '352 patent traces priority to a series of applications, including: (1) U.S. Application No. 372,692 filed on January 13, 1995; (2) U.S. Application No. 959,856 filed on November 12, 1992 (the " '856 application"), (3) U.S. Application No. 759,106 filed on September 6, 1991; (4) U.S. Application No. 215,602 filed on July 1, 1988; (5) U.S. Application No. 910,230 filed on February 6, 1986; (4) U.S. Patent Application No. 640,081 filed on August 8, 1984 ("the 1984 U.S. application"); (5) PCT Application PCT/DK83/00118 filed on December 9, 1983 ("the 1983 PCT application"). ('352 patent, col. 1 at ll. 4-16)

23. The '352 patent generally discloses a process to prepare a desired protein. (*See* '352 patent, col. 1 at ll. 17-19)

24. In particular, the '352 patent describes using an aminopeptidase, preferably DAP I, to cleave a pro-sequence containing an even number of amino acids thereby forming a desired protein. ('352 patent, col. 1 at ll. 56-60)

25. The '352 patent discloses nine examples. Examples 2-4 indicate that DAP I from Boehringer Mannheim was used to cleave the pro-sequence from the desired protein. None of the examples mention using DAP I from Sigma. ('352 patent, col. 4 at 11. 50-col. 5 at ll. 5)

26. The '352 patent includes two independent claims directed to biosynthetic ripe hGH.

27. Claim 1 recites:

> Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone.

('352 patent, col. 10 at ll. 7-9)

28. Claim 2 recites:

> Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.

('352 patent, col. 10 at 10-15)

29. In May 1997, plaintiffs filed a request for reexamination of the '352 patent based upon a substantial new question of patentability posed by various prior art references including U.S. Patent No. 4,755,465 (the "Gray '465 patent"), U.S. Patent No. 4,775,622 (the "Hitzeman '622 patent"), and U.S. Patent No. 4,745,069 (the "Mayne '069 patent"). (NNX 792 at NNG 0023024; NNG 0023047) Plaintiffs also sought to amend claims 1 and 2 and add new claim 3 as follows:

> ***4** Claim 1. (Amended) Biosynthetic ripe human growth hormone of at least 99% purity, which is free of contaminants from pituitary derived human growth hormone.
>
> Claim 2. (Amended) Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein, wherein the amino terminal extension is negatively charged, in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.
>
> Claim 3. Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone, said human growth hormone being of sufficient purity to be administrable to humans.

(*Id.* at NNG 0023051) (bolded text shows proposed amendment to claims 1 and 2)

30. In August 1997, the examiner denied the request for reexamination, concluding that the cited prior art did not raise any substantial new questions of patentability. The examiner stated:

> The [c]laims of the Dalboge et al. patent, for which reexamination is requested, are directed to ripe human growth hormone (hGH) that is free of pituitary contaminants. The patent defines ripe hGH as having 191 amino acids.... Gray et al. do not claim ripe hGH and no interference of claimed subject matter is apparent.... [B]ecause Mayne et al. do not cleave the N-terminally extended [growth hormone] with enterokinase and because such cleavage would be expected to remove the N-terminal extension and truncate hGH at amino acid position 172, Mayne et al.

do not teach ripe [growth hormone] ... Hitzeman et al. did not sequence the entire hGH that was secreted from yeast but sequenced only the N-terminal of secreted hGH. The immunoassay used to detect the secreted hGH would not be expected to differentiate between hGH truncated at the C-terminal by yeast proteases and ripe hGH ... and therefore this argument is sufficient to void Hitzeman et al. as raising a substantial new question of patentability.
(*Id.* at NNG 0023105)

E. BTG's '248 Application

31. The '248 application was filed on February 13, 1998. (DE 1002 at 1)

32. The '248 application claims priority to U.S. Application No. 641,488 (the " '488 application") filed on August 16, 1984. (*Id.*)

33. The '248 application generally discloses a method of removing N-terminal amino acid residues from a eucaryotic polypeptide synthesized in a foreign host using an aminopeptidase enzyme. (*Id.* at 174)

34. More specifically, the '248 application discloses using *Aeromonas* aminopeptidase to remove an N-terminal methionine residue and its adjacent leucine residue from a fusion protein for hGH. (*Id.*)

35. Claim 61 of the '248 application [FN1] recites:

> FN1. Claim 61 is identical to claim 1 of the '352 patent.

> Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone.
> *Id.* at 168.

36. Claim 62 of the '248 application [FN2] recites:

> FN2. Claim 62 is identical to claim 2 of the '352 patent.

> Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.
> ***5** *Id.*

37. Claim 63 of the '248 application recites:
Bacterially-derived authentic human growth hormone.
Id. at 171.

38. Claim 64 of the '248 application recites:
Recombinant authentic human growth hormone produced by (a) expressing in a bacterium human growth hormone having a methionine residue followed by a leucine residue added to a the N-terminus of authentic human growth hormone, (b) enzymatically removing the amino terminal methionine and leucine and (c) recovering recombinantly produced authentic human growth hormone.
Id.

39. On February 13, 1998, BTG filed a request for an interference between the '248 application and the '352 patent pursuant to 37 C.F.R. § 1.607. [FN3] (DE 1002 at 62)

> FN3. An interference is an *inter parte* proceeding conducted by the Board to resolve questions of priority of an invention. 35 U.S.C. § 135(a).

40. On April 8, 1999, the examiner determined that all claims were allowable, but suspended the ex parte prosecution pending a decision regarding BTG's request for an interference. (*Id.* at 16)

41. On July 7, 2000, the administrative patent judge granted BTG's request for an interference pursuant to 35 U.S.C. § 135(a). (*Id.* at 97)

F. Novo Patent Filings Prior to the '352 Patent

a. The 1982 Danish Application

42. Danish Application No. 5493/82, entitled "A Process For Preparing Ripe Proteins From Fusion Proteins Synthesized in Pro- or Eukaryotic Cells," was filed on December 10, 1982 ("the 1982 Danish application"). (BTX 3)

43. The 1982 Danish application is directed to a process for preparing ripe proteins by, first, expressing in pro- or eukaryotic cells a DNA segment, which codes for the synthesis of a fusion protein and, then, converting the fusion protein produced from the DNA segment to the ripe protein in vitro. (*Id.* at 7-8)

44. The 1982 Danish application generally describes four procedures for preparing desired ripe proteins from fusion proteins. (*See id.* at 8-10) To this end, the 1982 Danish application does not recite any information concerning the reaction conditions, such as pH, time, temperature, or enzyme-to-substrate ratio, to be used for the enzymatic

cleavage reactions. The 1982 Danish application merely states: "This cleavage reaction is to be optimized with respect to time and enzyme concentration as, in the case of prolonged incubation, aminopeptidase I can also hydrolyze amino acids of the desired product." (*Id.* at 9)

45. Similarly, the 1982 Danish application does not specify the identity, length, or sequence of the amino acid pro-sequence. The only guidance provided is that when formyl methionine or methionine is not part of the pro-sequence, the C-terminal amino acid, which is directly bonded to the N-terminal amino acid of the desired protein, must be proline, unless the desired protein itself contains proline as the N-terminal or next-to-the-outermost N-terminal amino acid. (*Id.* at 10) Besides this information, the 1982 Danish application discloses only that "X is an arbitrary amino acid" when the pro-sequence is X-proline and that "the DNA sequence corresponding to this pro-sequence may be selected from among the large number of naturally occurring sequences or may be synthesized *in vitro* when the structure at the nucleotide and amino acid level is known." (*Id.* at 8, 9)

***6** 46. Lastly, the 1982 Danish application states "proteases ... and in particular aminopeptidases" are used to cleave pro-sequences in fusion proteins. (*Id.* at 8) The 1982 Danish application identifies AP I and LAP as suitable aminopeptidases, but does not disclose a particular supplier of LAP. (*Id.* at 9, 10)

47. The 1982 Danish application does not contain any examples or experimental data. (*Id.*)

48. The 1982 Danish application contains eight claims directed to processes for preparing ripe proteins. (*Id.* at 11-13)

49. Claim 1 recites a process to prepare ripe proteins using recombinant DNA technology. (Id. at 11) Claim 1 does not disclose a particular enzyme to cleave the pro-sequence, but states that the enzyme "stops the cleavage of the amino acids of the pro-sequence one step before proline." (*Id.*)

50. Claim 7 is dependant upon claim 1 and specifies LAP as the cleavage enzyme. (*Id.* at 12)

51. Claim 8 is dependent upon claims 1-7 and discloses a process to prepare hGH wherein the pro-sequence is specifically phenyl alanine proline. (*Id.* at 13)

b. The 1983 PCT Application

52. The 1983 PCT application, entitled "A Process for Preparing Ripe Proteins from Fusion Proteins, Synthesized in Pro- or Eukaryotic Cells," was filed on December 9, 1983 and claims priority to the 1982 Danish application. (BTX 11)

53. The named inventors include Thorkild Christensen, Per Balschmidt, Hans Henrik Dahl, and Kim Hejnaes. (*Id.*)

54. The 1983 PCT application mirrors the 1982 Danish application, except that the 1983 PCT application includes additional disclosure about the amino acid sequence of the fusion protein and five examples that were not part of the 1982 Danish application. (*Id.* at 6-7, 9-14) The 1983 PCT application also prefers LAP as the aminopeptidase; the 1982 Danish application did not make this preference. (*Id.* at 6)

55. Example 1 relates to the synthesize of hGH and describes the experimental procedures used to make hGH in the past tense. (*Id.* at 9) First, Example 1 discloses that the fusion protein having methionine (Met), leucine (Leu), alanine (Ala), valine (Val), and serine (Ser) ("MLAVS") as the pro-sequence was expressed and evaluated to be greater than 98% pure. (*Id.*) Second, Example 1 indicates that disulfide bridges in the purified fusion protein were reduced and that the resulting disulfide bonds were broken via S-carbamidomethylation as described in a literature reference. Third, Example 1 states that the purified, reduced, and S-carbamidomethylated fusion protein was treated with LAP as described by D.H. Sprekman and A. Light in the presence of urea and aprotinin. (*Id.* at 11) Example 1 does not identify a supplier of LAP. Finally, Example 1 discloses that reaction mixture was fractionated by ion exchange chromatography and that the isolated hGH was determined to be 98% pure. (*Id.*)

56. Dr. Henrik Dalboge wrote the first part of Example 1 (i.e., expression of hGH with the MLAVS pro-sequence), and Mr. Thorkild Christensen wrote the second part of Example 1 detailing the cleavage and purification steps. (*See* D.I. 64 at 745-46) Mr. Christensen admitted at trial that Dr. Dalboge used past tense to describe the expression step because he actually performed this experimentation. Mr. Christensen also admitted that he had not performed the cleavage and purification steps at the time the 1983 PCT application was filed. (*See id.* at 747)

***7** 57. Example 2 relates to the synthesis of human proinsulin in yeast wherein the pro-sequence was, in order, methionine, leucine, valine, alanine, gylcine, and proline. (BTX 11 at 12) Example 2 discloses that LAP was used to cleave the pro-sequence from human proinsulin. (*Id.*) Example 2, like Example 1, does not

identify a supplier of LAP. Example 2 indicates that isolated human proinsulin was "better than 90% pure." (*Id.* at 12-13)

58. Examples 3-5 relate to the enzymatic cleavage of small peptides with LAP. (*Id.* at 13-14) Example 3 discloses that the reaction was conducted at a pH of 8.5 and that LAP from Sigma was utilized to cleave the pro-sequence from the small peptide. (*Id.* at 13) Examples 4-5 do not provide a supplier of LAP or discuss a specific pH for the cleavage reaction. (*Id.* at 14)

59. The 1983 PCT application contains four claims. (*Id.* at 15-16)

60. Claim 1 is directed to a process for preparing ripe proteins by enzymatic cleavage of a fusion protein with an aminopeptidase. (*Id.* at 15)

61. Claim 2 is dependent upon claim 1 and discloses that LAP is the aminopeptidase. (*Id.*)

62. Claim 3 is dependent on claims 1 or 2 and specifies that hGH is the desired protein. (*Id.* at 16)

c. The 1984 U.S. Patent Application

63. The 1984 U.S. application, entitled "Process for Preparing Ripe Proteins from Fusion Proteins, Synthesized in Pro- or Eukaryotic Cells," was filed on August 8, 1984 and claims priority to the 1983 PCT application and the 1982 Danish application. (NNX 322 at 1)

64. The 1984 U.S. application is identical to the 1983 PCT application; it contains the same disclosure and same five examples. [FN4] (*Id.* at 16-33)

> FN4. At filing, Novo attempted to add a sixth example to the 1983 PCT application describing the production of hGH by cleaving the pro-sequence methionine, phenylalanine, glutamic acid, and glutamic acid ("MFEE") from the fusion protein MFEE-hGH using LAP. (Civ. No. 02-235-SLR; Paper 124 at 9) The cleavage reaction was performed at a pH of 5.0, and acetamide was added to the reaction mixture. (Civ. No. 02-235-SLR; NNX 332 at 39-40) The PTO refused this addition.

65. During the *ex parte* prosecution, Novo abandoned the 1984 U.S. application by failing to respond to the Examiner's letter dated July 8, 1987. (NNX at 81)

G. Novo's Experimentation to Produce hGH

a. After Filing the 1982 Danish application on December 10, 1983 and Before Filing the 1983 PCT Application on December 9, 1983

66. After filing the 1982 Danish application, Novo dedicated a research group, called the "biosynthetic hGH group" or "B-hGH group," to prepare hGH using recombinant DNA techniques. (D.I. 60 at 145)

67. On March 14, 1983, the B-hGH group held their initial meeting at which time they decided to use LAP to synthesis hGH. (*Id.* at 145-46; BTX 5)

68. On September 12, 1983, the B-hGH group held their fifth meeting. (D.I. 60 at 147-149; BTX 6) The meeting minutes reveal that the group performed "proof of principle work." That is, to test whether the Y-pro stop strategy was a viable way to produce hGH, they made small peptides consisting of the first four amino acids of hGH preceded by an amino acid extension and then attempted to cleave the extension with LAP purchased from Sigma. These experiments were not successful; LAP completely degraded the amino acid extension as well as the first four amino acids of hGH. (D.I. 60. at 148) As a result of this degradation, the group decided to repeat the experiment using LAP purchased from Boehringer. (*Id.*; BTX 6 at D020672) They also decided to optimize the cleavage time and amount of enzyme. (*Id.*)

***8** 69. On September 26, 1983, the B-hGH group held their sixth meeting. (BTX 7) The minutes indicate that the group repeated the proof of principle work using slightly longer amino acid extensions and LAP purchased from Boehringer. (D.I. 60 at 150; BTX 7 at D020675) These experiments showed mixed results; correct cleavage occurred, but was accompanied by "inexplicable degradation." (D.I. 60 at 150; BTX 7 at D020675) The group decided to purify the LAP preparation to eliminate any contaminants. (*Id.* at 150; BTX 7 at D0202675)

70. On October 31, 1893, the B-HGH group held their seventh meeting. (BTX 1313) The minutes state:

> According to Sundin[, Novo's patent attorney,] this application [referring to the 1982 Danish application] is very weak. Especially the application is wanting of good practical examples besides the results with small peptides already present ... It would be best if we could use the modified B-hGH with the leucin aminopeptidase. This involves culturing and purification of the leucin aminopeptidase (as it perhaps also contains trypsin and chymotrypsin-like proteases).

(*Id.* at NNDEII 002539) The minutes also state: "JWH/THC have set up a pH-static system to enable easy supervision of the leucin aminopeptidase activity. The

enzyme has an activity maximum at pH 8.4--8.6." (*Id.*)

71. In late November or early December 1983, Novo scientists attempted to synthesize hGH by cleaving the pro-sequence MFEE from the fusion protein MFEE-hGH. The experiment resulted in partial cleavage of one or two amino acid residues from the N-terminus; ripe hGH was not produced. (D.I. 64 at 711-12)

72. When Novo filed the 1983 PCT application on December 10, 1983, the B-hGH group had not successfully prepared hGH with LAP using recombinant DNA technology. (*See* D.I. 60 at 159; *see also* D.I. at 790)

b. After Filing the 1983 PCT Application on December 9, 1983 and Before Filing the 1984 U.S. Application on August 8, 1984

73. On January 19, 1984, the B-hGH group held their eighth meeting. (BTX 12) The minutes report that Novo scientists tested three different pro-sequences, namely (1) Met-PHe-Glu-Glu, (2) Met-Leu-Ala-Leu-Glu, and (3) Met-Leu-Ala-Val-Ser, but were not successful in completely cleaving any one of them from the fusion protein. [FN5] (*Id.*; D.I. 60 at 163) The group agreed to optimize the incubation conditions for LAP. The group likewise decided to discontinue preparing additional pro-sequences until the activity and the specificity of LAP were better qualified. (*Id.* at D020683)

FN5. Notably, the pro-sequence, Met-Leu-Ala-Val-Ser, was described in Example 1 of the 1983 PCT application as being cleaved to yield hGH of 98% purity. (*See infra,* Section II, G)

74. On February 13, 1984, the B-hGH group held their ninth meeting. (BTX 15) The minutes reflect that the group investigated the incubation conditions for LAP, including incubation time/activity, ion strength/activity, and proportionality of the enzyme amount/activity. In light of this investigation, they opted in the spring of 1984 to terminate all experiments involving the digestion of pro-sequences. They decided to embark on a new approach that relied on the *E. coli* bacteria itself to cleave the pro-sequence, thereby eliminating the need for an enzyme to perform the cleavage. (*Id.* at B020687; D.I. 60 at 165-66)

***9** 75. On March 7, 1984, the B-hGH group held their tenth meeting. (BTX 17) The minutes indicate that pro-sequence cleavage with LAP was still not successful. To this end, the scientists reported that LAP lacks specificity under certain conditions and is "somewhat unstable." (*Id.* at D020692; D.I. 60 at 168-69) The minutes also indicate that Novo expected "to have a good impression whether it is practically possible to degrade presequences [FN6] with LAP in about 1 month." (BTX 17 at D020692) The minutes further note that Novo's new approach employing bacteria to cleave pro-sequences showed success as the *Pseudomonas* bacteria was able to cleave a pro-sequence from "pre-hGH." (*Id.*)

FN6. The court understands that the term "presequence," as used in the March 7, 1984 B-hGH group meeting minutes, has the same meaning as the term "pro-sequence."

76. On March 7, 1984, Novo first synthesized hGH by cleaving the MFEE pro-sequence from the fusion protein MFEE-hGH using LAP from Sigma (Freeze-drying Sigma 112F-8151). [FN7] (D.I. 64 at 726-728; BTX 468A at D025808) Unbeknown to Novo at the time of this experiment, the particular batch of LAP was contaminated with the DAP I. (D.I. 60 at 170) The reaction also was conducted at a pH much lower than that used in previous experiments due to the types and amounts of additives. (*Id.* at 171-172) In this regard, Novo scientists planned to run the degradation reaction at pH 8.5, the optimal pH of LAP. (D.I. 64 at 799-800, 803; BTX 468A at D025808) Nevertheless, the scientists unintentionally lowered the pH of the reaction mixture to the range optimal for DAP I by adding 158.4 mg of acetamide. [FN8] (D.I. 60 at 172, 175) The scientists, however, were not aware of this drop in pH. (D.I. 65 at 804)

FN7. In Example 1 of the 1983 PCT application, the pro-sequence contained five amino acid residues as opposed to the four amino acid residues found in the pro-sequence of the March 7, 1984 experiment.

FN8. On March 13, 1984, Novo scientists repeated the cleavage experiments using MFEE-hGH as the fusion protein with LAP from Sigma. The scientists varied the addition of acetamide to determine its effect on the reaction mixture. (*See* BTX 468A at D025822) In the first experiment, the pH was set in buffer, acetamide was added, and the pH was readjusted to 8.5. (*Id.*) In the second experiment, the pH was set in buffer and acetamide was added. The pH was not re-set. It measured 4.8. (*Id.*) In the third experiment, the pH was set at 8.6; no acetamide was added. (*Id.*)

77. Several months thereafter, Novo initiated a pilot scale production of ripe hGH using LAP from Sigma with alanine, glutamic acid ("AE") as the pro-sequence. [FN9] (D.I. 64 at 738-741; NNX 850)

FN9. The exact date of the first pilot batch is unclear from the record. While Novo's witness, Mr. Thorkild Christensen, testified that this pilot production occurred in the summer of 1984, the G-hGH meeting minutes report this pilot on March 18, 1985. In any event, it occurred several months after Novo's initial success in producing ripe hGH.

H. Novo's Identification of DAP I and Patent Filings Directed to the Use of DAP I to Produce hGH

78. On October 18, 1984, the B-hGH group held their twentieth meeting. (BTX 20) The minutes report that

> [i]t has been tried to degrade [methionine, alanine, glutamic acid] MAE-hGH with LAP from various firms. The Sigma preparation is the only functioning, however, Boehringer LAP has shown a very small activity. It has turned out that the active component in Sigma LAP presumably is not LAP but a 'contaminating' substance. Microsomal LAP has no activity. [Methionine, phenylalanine, glutamic acid] MFE-hGH and [methionine, leucine, glutamic acid] MLE-hGH cannot be degraded.

(*Id.* at D020740)

79. On February 7, 1985, Novo filed a Danish patent application, entitled "An Enzyme or Enzyme Complex Having Proteolytic Activity," directed to a "heretofore unknown proteolytic enzyme or enzyme complex" capable of cleaving a pro-sequence from a fusion protein of hGH and the use of said enzyme or complex to accomplish enzymatic cleavage (the "1985 Danish application"). [FN10] (DE 1005) The 1985 Danish application discloses that the enzyme or enzyme complex does not cleave phenylalanine from the N-terminus of hGH and has its maximum enzymatic activity in the pH range of 4.0 to 5.0, preferably 4.2 to 4.6. (*Id.* at 2) The 1985 Danish application also discloses that the enzyme or enzyme complex may be irreversibly inactive at a pH of 8.4 at 40C. (*Id.* at 3) The 1985 Danish application further discloses that the enzyme or enzyme complex is isolated from a leucine aminopeptidase containing aqueous extract of pork kidneys and with optimum activity at a pH range of 7 to 9. (*Id.*) The two examples specifically recite using LAP from Sigma (L-1503, lot 14F-8155).

FN10. Novo referred to this "unknown" enzyme as "AP-X." (D.I. 65 at 806)

***10** 80. On April 17, 1985, the B-hGH group held their twenty-eighth meeting. (BTX 25) The minutes reveal that Novo scientists suspected that AP-X was DAP I. "If our AP-X is the dipeptidyl peptidase I[,] it is commercially available. Various preparations will be bought and tested." (BTX 25 at D020790)

81. On February 6, 1986, Novo filed a PCT application PCT/DK86/00014, entitled "A Process for Producing Human Growth Hormone," directed to the process for producing hGH from amino terminal extended hGH using DAP I (the "1986 PCT application"). (BTX 28) This application claims priority to the 1985 Danish application. (*Id.*) The 1986 PCT application discloses that the amino acid extension must consist of an even number of amino acids because DAP I cleaves only dipeptidyl units. (*Id.* at 3) Additionally, the 1986 PCT application discloses five suitable amino terminal extensions. (*Id.* at 4-5)

82. On October 3, 1986, Novo filed U.S. Patent Application No. 06/910,230, entitled "Process For Producing Human Growth Hormone," directed to a process of producing hGH using DAP I ("the 1986 U.S. application"). This application claims priority to both the 1986 PCT Application and the 1985 Danish application. Over the next several years, Novo filed other U.S. applications describing the use of DAP I to produce ripe hGH. These applications eventually culminated in the '352 patent.

I. Novo's Statements Subsequent to the '352 Patent Concerning LAP

83. On October 11, 1989, during the *ex parte* prosecution of the 1986 U.S. application, the examiner rejected the claims as unpatentable over the Daum '329 patent. [FN11] (BTX 311 at 3)

FN11. The Daum '329 patent was filed on July 6, 1982 and claims priority to an application filed on May 29, 1980. (BTX 1373) The Daum '329 patent granted on September 24, 1985. Claim 13 discloses the use of LAP to cleave a fusion protein. (Daum '329 patent, col. 9 at ll. 60-62) Claim 15 recites using the process of Claim 13 wherein LAP is E.C. 3.4.11.1.

84. On April 11, 1990, in a response after final rejection, Novo distinguished the Daum '329 patent from the invention claimed in the 1986 U.S. application. Novo stated:

> Daum mentioned in column 4 that with LAP it is possible to 'split off N-terminal methionine from foreign proteins containing after the direct synthesis the sequence Met-Uvw-Pro, wherein Uvw can be any desired amino acid except for proline.' This shown in example 13 with the peptide Met-Gly-Pro-amide with the result: Gly-Pro-amide. This disclosure is in accordance with the prior art ... which discloses that LAP is useful for hydrolysis of small peptides.

> Although applicants have tested LAP with bacterially produced hGH, LAP has been shown not to be effective. The effectiveness of LAP seems to disappear as soon as peptides greater than about 50 amino acids are involved. In fact, Daum's examples are conspicuous by the relative absence of examples showing the effectiveness of LAP on larger peptides and Daum does not use bacterially produced protein or peptide in its examples.

(BTX 311 at 5) (emphasis in original)

85. On September 12, 1990, during the *ex parte* prosecution of the 1986 U.S. application, Novo filed a declaration on behalf of Jorli Ringsted, John Pedersen, and Thorkild Christensen, all of whom were inventors named on the '352 patent, detailing the ability of LAP to remove a pro-sequence from the fusion protein for hGH ("1990 Declaration"). (BTX 23) In the experiments described, the Novo scientists varied the pH of LAP, the amount of LAP used, the concentration of acetamide added to the cleavage mixture, and the supplier of LAP. In particular, the Novo scientists used LAP from Sigma (L1503, batch 14F-8155) in all examples, except example 5 where LAP from various suppliers was tested. In example 2, the Novo scientists compared the ability of LAP from Sigma to cleave the pro-sequences alanine, glutamic acid ("Ala-Glu") and MFEE from the fusion protein for hGH at select pHs. The Novo scientists found that Ala-Glu-hGH showed 100% conversion after 1-2 hours at pH 5.5, 75% conversion after 1 day at pH 6.5, 10% conversion after 1 day at pH 7.5, and 0% conversion after 1 day at pH 8.5. (*Id.*) The Novo scientists also found that LAP from Sigma was not able to cleave 100% of the pro-sequence MFEE from the fusion protein MFEE-hGH at pH 5.5 after 1 day. (*Id.*) In example 5, the Novo scientists compared seven LAP preparations from suppliers such as Sigma, Boehringer, Merck, Serva, and Worthington at a pH of 5.5. (BTX 22 at D021372; D.I. 65 at 942-944). The scientists concluded:

> ***11** It is shown that essentially only LAP-preparations from Sigma contain enzymatic activity able to convert Ala-Glu-hGH to mature hGH. LAP-preparations from Merck, Serva, and Worthington did not contain such enzymatic activity at all. It is thus likely that an enzymatic activity different from LAP-activity is contained in the Sigma preparations and to a certain degree in the Boehringer product which can convert Ala-Glu-hGH to mature hGH.

(BTX 23) In sum, the Novo scientists stated:

> The experiments show clearly that a pure LAP-preparation will not convert amino extended hGH to mature hGH. Only LAP-preparations with relevant impurities will have some effect depending upon the nature and amount of the impurity and of course this can lead to misunderstanding about the effect of LAP. (*Id.*)

86. On November 13, 1990, two months after Novo filed the 1990 Declaration in connection with the 1986 U.S. application, Novo filed a preliminary amendment during the prosecution of U.S. Patent Application No. 07/595,783 (the " '783 application"), an application that claims priority to the 1986 U.S. application. Novo stated:

> The Examiner has rejected the claims under 35 U.S.C. [§] 103 as allegedly being obvious from Brewer in view of Daum. By Declaration filed September 12, 1990, [a]pplicant showed that a pure LAP-preparation will not convert amino extended hGH to mature hGH, thereby supporting [a]pplicant's argument that Daum would not be effective to solve the problem solved by the claimed invention. In an [a]dvisory [a]ction dated September 18, 1990, the [e]xaminer erroneously stated that the [1990] [D]eclaration shows that commercial grade LAP as taught by Daum would have worked. In fact, the [1990] Declaration supports the proposition that it is not LAP, but another enzyme (apparently DAP I), which is responsible for the effectiveness of the Sigma product tested in the [1990] Declaration. The [1990] Declaration clearly shows that commercial grade LAP would not have worked. The only exception is a specific LAP product delivered by Sigma (and not shown to have been investigated by Daum) which contains another enzyme.

(BTX 246 at NNG 0024930)

87. On February 4, 1991 and March 27, 1991, the PTO issued office actions rejecting the claims of the '783 application over the published version of the 1983 PCT application. [FN12] (BTX 246 at NNG 0024935-36) On September 27, 1991, Novo argued in an amendment in response to the office actions that the 1983 PCT application was "inoperative" and was "clearly not enabling." (*Id.* at NNG 0024960) Novo stated:

> FN12. In the February 4, 1991 office action, the examiner specifically stated:
> The rejection of claims 1-6 and of new claims 7 and 8 under 35 U.S.C. [§] 103 as unpatentable over Brewer in view of Daum et. al. is maintained ... Note that the [1990 Declaration] and the remarks in the preliminary amendment filed 13 November 1990 has [sic] been considered but is [sic] not persuasive. It is pointed out that the [1990] Declaration and the remarks in the preliminary amendment clearly show by applicants' own results that a commercial preparation used without further purification would have contained the requisite enzymatic functionality as the commercial grade of LAP contains more than just LAP.... Claims

> 1-6 are rejected under 35 U.S.C. [§] 103 as unpatentable over the combination of the [1983 PCT application] and Daum et. al., and Callahan (Enzymes). The [1983 PCT application] disclose[s] using an aminopeptidase to cleave N-terminal residues from a polypeptide produced from *E. coli* containing and expressing heterologous DNA encoding human growth hormone ... One of ordinary skill in the art would have been motivated to use any other aminopeptidase as well as the preferred leucine aminopeptidase ... since using a "suitable amino peptidase" is suggested ... it is pointed out that the [1990] Declaration and the remarks in the preliminary amendment clearly show by applicants own results that a commercial preparation used without further purification would have contained the requisite enzymatic functionality as the commercial grade of LAP contains more than just LAP and would apparently have cleaved the polypeptide. The remarks with regard to the purity of LAP or of DAP I are not convincing in light of the claims which define the metes and bounds of the invention.
> (*Id.* at NNG 0024934-0024935)

As shown by the [1990] Declaration filed September 12, 1990, a pure LAP-preparation will not convert amino extended hGH to mature hGH. The [1983 PCT application] is thus inoperative. The [e]xaminer has erroneously maintained that the [1990] Declaration shows that commercial grade LAP would have worked. In fact, the declaration supports the proposition that it is not LAP, but another enzyme (apparently DAP I), which is responsible for the effectiveness of the Sigma product tested in the [1990] Declaration. The [1990] Declaration clearly shows that LAP would not have worked. The only exception is the specific "LAP" product delivered by Sigma which contains another enzyme. Certainly those of skill in the art cannot be said to be enabled to practice the invention disclosed in [the 1983 PCT application] if such enablement is dependent on the chance that they purchase "LAP" from a specific supplier. Accordingly, [the 1983 PCT application] is clearly not enabling.

***12** (*Id.*) (emphasis in original) Novo also asserted that the 1983 PCT application did not provide enough information about aminopeptidase enzymes, despite using the "suitable aminopeptidase" language, to guide one of ordinary skill in the art to DAP I. In this regard, Novo stated:

> The [1983 PCT application] relates specifically to the use of LAP to cleave N-terminal residues from a polypeptide produced in *E. coli*. The [e]xaminer maintains that [the 1983 PCT application] would have motivated the use of other aminopeptidases because it uses the language "a suitable aminopeptidase." However, this language is not sufficient to suggest that DAP I by itself would be effective in the [1983 PCT application] process.
> (*Id.*)

88. Novo stated in the published European Patent No. 0217814, the European equivalent of the '352 patent, that:

> In [the 1983 PCT application], a process for producing i.a. authentic hGH is suggested, wherein a biosynthetically formed N-terminal extended hGH is digested with an aminopeptidase, preferably leucine aminopeptidase (LAP) in order to cleave the extension. The extension consisted of arbitrarily selected amino acids which were removed by stepwise cleavage. However, this process did not work in practice with pure LAP.
> (DE 2016 at 3)

J. Novo's Statements During the European Opposition Filed by Eli Lilly and Company Involving LAP

89. In opposing European Patent No. 0217814, Eli Lilly and Company argued that the claims in the European Patent No. 0217814 were invalid on obviousness grounds in view of the 1983 PCT application and two other prior art references. (*See* BTX 36)

90. On December 5, 1991, Novo refuted this allegation by arguing that LAP, as disclosed in the 1983 PCT application, was inoperable. Novo stated:

> This prompted [Novo] to undertake a fractionation on the LAP from Sigma and it was verified that two different enzymatic activities were present, viz an activity converting Ala-Glu-hGH to hGH and an activity converting Leu-NH2 to Leu and NH3, the true LAP activity. Initially, the inventors believed that a new enzyme had been discovered, but further investigations of the "impurity" verified that the enzymatic activity was in fact DAP I. The presence of DAP I as an impurity in LAP had not been reported earlier.... The reason for the inoperability of LAP has not been found. Without wishing to be bound by any particular hypothesis, it could be assumed that due to the size of the hGH molecule and its tertiary structure the extension is oriented in a way that does not make it available to the digestion of the enzyme. Whatever the reason might be, the person skilled in the art might reasonably expect it to be a general limitation vs. aminopeptidases. [FN13]
>
> FN13. Novo offered this same argument to the Canadian Patent Office during the prosecution of

the Canadian Patent Application No. 520,332. (*See* BTX 69 at 4)

(*Id.* at NNG0025824-002525)

91. Novo also implied that a person of ordinary skill in the art attempting to cleave the pro-sequence from ripe hGH would be prejudiced by the disclosure concerning LAP found in the 1983 PCT application. Novo stated:

> ***13** A number of further characterizations were introduced in order to arrive at the invention as claimed in EP-B1-217814, characteristics which could not be adopted by a person skilled in the art from the very general teachings of [the 1983 PCT application] who also first had to overcome the prejudice created by the inefficiency of LAP.

(*Id.* at NNG0025825)

92. In summarizing its position regarding the inoperability of the process disclosed in the 1983 PCT application, Novo stated:

> [A]n attempt to reproduce [the 1983 PCT application] would also establish prejudice against the use of aminopeptidases for digestion of N-temrinal hGH extensions.

(*Id.* at NNG0025835)

93. Novo ultimately added the following statement about the 1983 PCT application to European Patent No. 0217814 to convince the European Patent Office that its claims were valid in light of the 1983 PCT application:

> In [the 1983 PCT application] a process for producing i.a. authentic hGH is suggested, wherein a biosynthetically formed N-t an aminopeptidase, preferably leucine aminopeptidase (LAP) in order to cleave the extension. The extension consisted of arbitrarily selected amino acids which were removed by stepwise cleavage. However, this process did not work in practice with pure LAP.

(BE 2016, page 3, 11. 33-36)

K. Novo Statements During U.S. Litigation Regarding LAP

94. In 1995, at a hearing in the Southern District of New York, Dr. Henrik Dalboge, one of the named inventors on the '352 patent, testified about Novo's efforts to produce ripe hGH. He particularly explained Novo's experimentation with the LAP enzyme.

> Q: Could you explain to us how the strategy at Nordisk Gentofte to produce authentic human growth hormone of 191 amino acids evolved?
> A: Yes. The strategy was to make use of an enzyme which is called leucine aminopeptidase. This is an enzyme which can say kind of, I don't know if you are familiar with PacMan, is able to remove from the end terminals of protein, one amino acid at a time and this process will stop when the bond to be cleaved encounters the amino acid proline. And since proline is the second amino acid in growth hormone, this enzymatic reaction should stop just at the very beginning of human growth hormone, giving rise to the mature product of 191 amino acids.
> Q: Did that strategy, using leucine aminopeptidase, work?
> A: Well, I would say that it was very hard to get this to work at all. We made several different amino terminal extended products, and tried to convert these products into mature human growth hormone, but without success. So we also--I'm sorry.
> Q: What did you do then?
> A: We also tried to make some small synthetic peptides that had the same extension or the same sequence as we had in some of our extended products and, in addition to that, a few other amino acids, and we saw that on these synthetic peptides the enzyme did work, but we couldn't get it to work on the extended growth hormone molecules. I don't know how many times I have been standing there when we did the analysis to see whether there were any indication of conversion going on, but we never really saw anything.

***14** (D.I. 62 at 634-35)

L. BTG's Statements About LAP

95. During the prosecution of U.S. Patent Application No.08/400,544, filed March 8, 1995 and entitled "Method of Removing N-Terminal Amino Acid Residues from Eucaryotic Polypeptide Analogs and Polypeptides Produced Thereby," BTG submitted a declaration prepared by Dr. Elhanan Ezra (the "Ezra Declaration"). Dr. Ezra compared the ability of LAP from Sigma with the ability *of Aeromonas* aminopeptidase to cleave the methionine amino acid pro-sequence from the fusion protein Met-hGH. (NNX 270) The results in Table 2 indicate that Sigma LAP released 16.6% of the Met from Met-hGH when a 1:10 enzyme:substrate ratio was used under a pH of 8.5. (*Id.*, Appendix B at 5) Dr. Ezra recognized: "[B]oth aminopeptidases were active, but differed greatly in their specificity for substrate and in their optimal assay conditions." (*Id.*, Appendix B at 4) Dr. Ezra concluded that "[t]he experiments unequivocally demonstrate that *Aeromonas* aminopeptidase is significantly and unexpectedly much more efficient than the leucine aminopeptidase enzyme used by [the 1983 PCT Application] and Daum et al. in removing N-terminal methionyl groups from two different polypeptides." [FN14] (*Id.* at ¶ 7)

FN14. The court notes that the Board did not

> even consider the Ezra Declaration in its decision. "We also need not and have not considered the Ezra testing ... in making our decision." (Paper 124 at 36-37)

96. Dr. Ezra testified at trial that he did not review the raw chromatographic data that led to the results presented in the Ezra Declaration prior to filing this document. (D.I. 65 at 1009, 1015) Dr. Ezra instead testified that he reviewed a draft report prepared by a scientist working under his supervision. (*Id.* at 1009) Dr. Ezra clarified that his assistant looked at the raw data, reconciled the specific retention times shown in the chromatogram, and calculated the specific cleavage efficiencies reported in Table 2 of the Ezra Declaration. (*Id.*)

97. Dr. Ezra testified that when he reviewed the raw chromatographic data for the first time prior to his deposition, he found the data was inconclusive for several reasons: (1) LAP and the fusion protein both produced a peak very near the retention time characteristic for methionine, making it impossible to distinguish the peak for methionine from that due to LAP and/or the fusion protein; (2) the data were below the calibration curve; and (3) the peak allegedly due to methionine was broad and poorly resolved. (*Id.* at 1008, 1023- 24)

M. Statements Regarding Example 1

98. During the *ex parte* prosecution of the '856 application, following an interview with the examiner wherein the examiner requested Novo to point out "where in the priority documents the enablement is present," Novo's in-house patent attorney directed the examiner's attention to several sections of the 1983 PCT application, including Example 1. [FN15] (*See* BTX 65 at NNG 0023546-47) Specifically, Ms. Cheryl Agris, Novo's in-house patent attorney, stated:

> FN15. The court observes that the examiner did not specifically raise the issue of enablement in the office action. (*See* BTX 65 at NNG 0023528-32). Novo, nevertheless, opted to comment on it in responding to the office action.

> Applicants also assert that an enabling disclosure of the invention claimed in the instant application is provided in the priority application. Attached hereto ... is a copy of [the 1983 PCT application], which corresponds to the [1982 Danish application], filed December 10, 1982.... Furthermore, Example 1 ... of [the 1983 PCT application] is specifically directed to hGH.

***15** (*Id.*) Later, in a March 17, 1994 office action for this same application, the examiner *sua sponte* raised Example 1 in connection with Novo's priority claims. The examiner observed:

> It appears that the instant invention and that disclosed in the [1983 PCT application] are not the same. Example 1 of [the 1983 PCT application] teaches that the hGH will be extended with Met-Leu-Ala-Val-Ser and this fusion protein expressed in *E. coli,* reduced, alkylated, and exposed to leu-aminopeptidase. These variables are different than those of the instant invention.

(*Id.*)

99. Novo did not inform its experts, Dr. Kenneth Walsh and Dr. Lydia Villa-Komaroff, that Example 1 contained prophetic data instead of actual experimental results as to the cleavage and purification steps until shortly before the patent infringement action. (D.I. 65 at 932-33) To this end, Dr. Walsh, who focused much of his work on the 1982 Danish application and the 1983 PCT application, was deposed two weeks prior to the start of trial and was unaware that the cleavage steps had not been performed. (D.I. 65 at 932) Dr. Walsh, in fact, testified that he was confident that Example 1 had been performed at his deposition and responded to deposition questions while under this impression. (D.I. 65 at 969-70) Similarly, Dr. Villa-Komaroff testified during her deposition for the interference proceeding that she thought Example 1 represented actual results. (D.I. 62 at 602-604; BTX 343 at 84)

N. The Interference Proceeding

100. On July 7, 2000, the PTO declared a patent interference between the '248 application and the '352 patent and designated the inventors of the '248 application as the "Junior Party" or "Party Blumberg" and the inventors of the '352 patent as the "Senior Party" or "Party Dalboge." (Paper 1) In the Notice Declaring Interference, the PTO accorded the '352 patent the benefit of priority of the filing date of the 1984 U.S. application (i.e., August 8, 1984). (*Id.*)

101. The PTO defined a single interference count directed to a composition of matter according to claims 1 or 2 of the '352 patent or claims 61, 62, 63, or 64 of the '248 application. [FN16] (*Id.*) Specifically, the count was defined as follows:

> FN16. "A count defines the interfering subject matter between two or more applications or between one or more applications and one or more patents." 37 C.F.R. § 1.601(f). "Each application must contain, or be amended to contain, at least one claim that is patentable over the prior art and corresponds to each count. All claims in the applications which define the same

> patentable invention as a count shall be designated to correspond to the count." 37 C.F.R. § 1.603.

A composition of matter according to claims 61, 62, 63, or 64 of Blumberg (09/023,248)
or
A composition of matter according to claims 1 or 2 of Dalboge (5,633,352).
(*Id.*) [FN17]

> FN17. The parties agree that the count covers hGH in a mixture with "other uncleaved or partially cleaved products." (D.I. 85 at 15) BTG does not agree that the count requires the hGH to be biologically active, as argued by Novo. Nevertheless, BTG has agreed to accept this reading of the count for purposes of the instant appeal. (*Id.*)

102. The Party Blumberg initially filed one preliminary motion under 37 C.F.R. § 1.633(g) attacking the benefit of the August 8, 1984 filing date accorded to the Party Dalboge for the '352 patent. [FN18] (Paper 24) The Party Blumberg sought a ruling that the '352 Patent is not entitled to the August 8, 1984 filing date because the 1984 U.S. application failed to satisfy the conditions of 35 U.S.C. § 120. [FN19] More specifically, the Party Blumberg argued that the invention defined by the claims of the '352 patent, which corresponds to the sole count of the interference, was not described in the 1984 U.S. application in sufficient detail to enable one of ordinary skill in the art to make and use the invention as required by 35 U.S.C. § 112, first paragraph. [FN20] (*Id.*) In other words, the Party Blumberg argued that ripe hGH, the subject matter of the count, could not be produced with the LAP as disclosed in the 1984 U.S. application.

> FN18. Section 1.633(g) entitles a party to file a "motion to attack the benefit accorded an opponent in the notice declaring the interference of the filing date of an earlier filed application." 37 C.F.R. § 1.633(g).
>
> FN19. Under 35 U.S.C. § 120,
> [a]n application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.
>
> FN20. The nature of the Party Blumberg's preliminary motion is clearly premised on patentability grounds, despite being filed under 37 C.F.R. § 1.633(g). The Party Blumberg should have filed its preliminary motion under either 37 C.F.R. § 1.633(a) or 37 C.F.R. § 1.635. Section 1.633(a) entitles a party to file a "motion for judgment against an opponent's claim designated to correspond to a count on the ground that the claim is not patentable to the opponent." Alternatively, section 1.635 entitles a party to file a miscellaneous motion for an order "relating to any matter other than a matter which may be raised under [37 C.F.R. §] 1.633 or [37 C.F.R. §] 1.634." Nonetheless, because (1) the court considers the Party Blumberg's mistake to be one of procedure rather than substance; (2) the Party Blumberg raised the substance of its motion concerning enablement during the interference proceeding; and (3) the Board decided the question of enablement, the court shall address the Party Blumberg's argument concerning whether the invention defined by the claims of the '352 patent was described in the 1984 U.S. application in sufficient detail to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

***16** 103. The Party Dalboge filed seventeen preliminary motions. (Papers 27- 43) For preliminary motion 3, the Party Dalboge requested that the PTO accord it the benefit of the filing dates of the 1983 PCT application filed on December 9, 1983 and the 1982 Danish application filed on December 10, 1982 pursuant to 37 C.F.R. § 1.633(f) and § 1.637(a), (d). [FN21] (Paper 29) The Party Dalboge's remaining preliminary motions generally concerned the patentability of the claims of the '488 application and were filed pursuant to 37 C.F.R. § 1.633(a).

> FN21. Section 1.633(f) entitles a party to file a "motion to be accorded the benefit of the filing date of an earlier filed application."

104. After the Party Dalboge's filing, the Party Blumberg filed three additional preliminary motions. In preliminary motion 2, the Party Blumberg sought to amend claims 61 and 62 and to add new claims to the '248 application pursuant to 37 C.F.R. § 1.633(c)(2). [FN22] (Paper 48) In